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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,656	10/24/2003	Igor Dozmorov	OMRF:013US	9649

7590 09/01/2009

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EXAMINER	
SKOWRONEK, KARLHEINZ R	
ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
09/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,656	DOZMOROV ET AL.	
	Examiner	Art Unit	
	KARLHEINZ R. SKOWRONEK	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9 and 11-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,9 and 11-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 23 July 2009 has been entered.

Claim Status

Claims 1, 3-7, 9, and 11-13 are pending.

Claims 2, 8, and 10 are cancelled.

Claims 1, 3-7, 9, and 11-13 have been examined.

Claims 1, 3-7, 9, and 11-13 are rejected.

Priority

This application claims the benefit of Provisional Application No. 60/ 420,826 filed on 24 October 2002.

Claim Rejections - 35 USC § 112

Response to Arguments

Applicant's arguments, see Remarks p. 7, filed 20 October 2008, with respect to the rejection of clams 1, 3-9, and 11-13 as indefinite under 35 USC 112 have been fully

considered and are persuasive. The rejection of claims 1, 3-9 and 11-13 has been withdrawn in view of the amendments to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3-6, 9, and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu (IDS file 2/27/04, Entry C13), in view of Shaffer (Annual Review of Psychology, Vol. 46, p. 561-584, 1995), in view of Nath et al. (Br J Clin Pharmacol, Vol. 52, p. 671-680, 2001), in view of Cole et al. (Prenatal Diagnosis, Vol. 19, p. 351359, 1999) and in view of deGroot et al. (Analytica Chimica Acta, Vol. 446, p. 71–83, 2001).

The claims are directed to a method of associative analysis comprising the collection of a plurality of expression profiles from a control and experimental group; normalizing the control and experiment groups relative to the background; adjusting the expression profiles by rescaling the control and experimental groups to an average of the control group; identifying similarly and differentially expressed genes, the differentially expressed genes are identified using a paired T-Test and an "associative T-Test"; determining a classification for the identified differentially expressed genes where genes identified by the T-test but not the Associative T-test are likely false positives, gene identified by the T-test and the associative T-test are real positives and genes identified by the Associative T-test but not the T-Test are potential positives; and outputting the classified real positives to a user. In some embodiments, the adjusting expression profiles further comprises regression analysis. In some embodiments, adjusting further comprising selected equally expressed genes as a homogenous family of genes with normally distributed residuals measured as deviations from a regression line that is calculated against an average profile.

Wu shows a method of analyzing gene expression profiles. Wu et al. shows the collection of a plurality of expression profiles from a control and experimental group (figure 1 and p. 55, col. 1). Wu et al. shows normalizing the control and experimental profiles (p. 56, col. 1) relative to background. Wu shows that expression profiles are scaled to an average of the control by scaling the control by $\sqrt{\beta}$ and the experimental by $\frac{1}{\sqrt{\beta}}$ (p. 56, col. 1). Wu shows that differentially expressed genes are identified using the T-test (p. 58, col. 1). In some embodiments, Wu shows that adjusting expression profiles further comprise regression analysis (p. 55, col. 2). In some embodiments, Wu shows that adjusting further comprises selected equally expressed genes as a homogenous family of genes with normally distributed residuals measured as deviations from a regression line that is calculated against an average profile (p. 56, col. 2). Wu shows that lower values for variability lead to higher T values and a larger number of false positives suggestive of the comparison of values for variability. Wu shows the F-test is a comparison of variances similar to the T-test as comparison of means (p. 60, col. 1). Wu shows the F-test is useful for identifying genes that are overexpressed or underexpressed in any one of several conditions (p. 60, col. 1). Wu shows that the F-test identified genes are retested (p. 60, col. 1). Wu shows an embodiment in which outliers are removed (p.57, col. 2). In some embodiments, the reference group of genes is determined by an F-test (p. 60, col. 1).

Wu does not show an “associative T-test” that is T-test of residuals, determining a classification for the identity of differentially expressed genes where genes identified

by the T-test but not the Associative T-test are likely false positives, gene identified by the T-test and the associative T-test are real positives and genes identified by the Associative T-test but not the T-Test are potential positives.

Cole et al. shows that true positives are identified by significant T-test and F-test statistics (p. 353, col. 2). Cole et al. shows that true negatives are identified by lack of significant T-test and F-test values (p.353, col. 2).

Nath et al. shows a T-test of residuals, reading on an associative T-test (p. 673, col. 2). Nath et al. shows the T-test of residuals is a metric used to evaluate the most appropriate model for the data (p. 673, col. 2).

Shaffer shows that when multiple pairwise T-tests are considered, the probabilities of false positives is additive, thereby reducing the power for testing individual hypotheses (p. 569). Shaffer shows that multistage test procedures; that is, also performing the F-test, overcomes the problems of multiple pairwise comparisons (p. 569). Shaffer suggests that potential positives can be detected if only the F-test is significant (p. 574). Shaffer shows that type I error is also known as a false positive classification (p. 566). Shaffer shows that in cases where multiple comparisons are performed, heterogeneity in the variance becomes a more serious concern. Shaffer points out that the variance of a particular comparison may be badly biased by the use of a common estimated value (p. 577). Shaffer's concern is interpreted as a suggestion for classification of false positive if the T-test is significant but the F-test is not.

Wu in view of Cole et al. in view of Nath et al. and in view of Shaffer do not show the diminishing or excluding the influence of outliers.

deGroot et al. is directed to the application of Principal Component Analysis (PCA) to a detect outliers in data. deGroot et al. shows that data is preprocessed to scale the data by mean-centering (p. 78, col. 2). deGroot et al. shows the pre-processed data used to perform PCA to detect outliers (p. 78, col. 2). deGroot et al. shows outliers have an effect on PCA and are removed, reading on outlier exclusion (p. 78, col. 2- p. 79, col. 1). deGroot et al. shows PCA is repeated until no more outliers are excluded (p. 79, col. 1). deGroot et al. shows that by removing outliers PCA is easier.

It would have been obvious to one of ordinary skill in the art to modify the gene analysis method of Wu with the combination analysis of T-test and F-test as described by Cole et al. and Shaffer because all the claimed elements were known, in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of the invention. It would have been further obvious to one of ordinary skill in the art at the time of invention to further modify the combination analysis of Wu et al. in view of Schaffer and in view of Cole et al. with the T-test of residuals of Nath et al. because Nath et al. shows it beneficially provides for the selection of the most accurate model. It would have been further obvious to one of ordinary skill in the art at the time of invention that a combination of the T-test and the T-test of residuals are indicators of likely true positive, false positives and potential positives because a significant T-test indicates a correlation greater than would be expected to occur randomly. The T test of the residuals indicates the how well the model correlates to the observed data. The paired

T-test indicates how well a variable correlates with the outcome. It would have further obvious to one of ordinary skill to exclude or diminish the influence of outliers in the method of gene analysis of Wu et al. in view of Cole et al. and in view of Shaffer by modifying the method with the iterative removal of outliers from the data of deGroot et al. because deGroot et al. shows removing the influence of outliers simplifies PCA by eliminating the data masking effect of the outliers.

Response to Arguments

Applicant's arguments filed 23 July 2009 have been fully considered but they are not persuasive. Applicant argues that Wu, in view of Shaffer, in view of Cole et al. and deGroot et al. do not show a T-test of residuals. This is not persuasive because Nath et al. shows a T-test of residuals (p. 673, col. 2).

Claims 1 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu, in view of Shaffer, in view of Nath et al., in view of Cole et al. and deGroot et al. as applied to claims 1, 3-6, 8-9, and 11-13 above, and further in view of Jensen et al. (Bioinformatics, Vol. 16, No. 4, P. 326-333, 2000).

Claim 7 is directed to a method of array analysis that further comprises a reference group that has residuals approximating Kolmogorov-Smirnov criterion.

Wu, in view of Shaffer, in view of Nath et al., in view of Cole et al. and deGroot et al. as applied to claims 1, 3-6, 8-9, and 11-13 above shows a method of array analysis.

Wu, in view of Shaffer, in view of Nath et al., in view of Cole et al. and deGroot et al. as applied to claims 1, 3-6, 8-9, and 11-13 above do not show a Kolmogorov-Smirnov criterion applied to a reference group.

Jensen et al. shows a Kolmogorov-Smirnov (K-S) criterion applied to a reference group (p. 328, col. 1). Jensen et al. shows that the K-S has the advantage of finding patterns without the need for data clustering (p 332, col. 1).

It would have been obvious to one of ordinary skill in the art at the time of invention to modify the method for array analysis of Wu, in view of Shaffer, in view of Nath et al., in view of Cole et al. and deGroot et al. as applied to claims 1, 3-6, 8-9, and 11-13 above with the K-S criterion of Jensen et al. because Jensen et al. suggests that the K-S criterion has the advantage of finding patterns without the need for data clustering.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KARLHEINZ R. SKOWRONEK whose telephone number is (571)272-9047. The examiner can normally be reached on 8:00am-5:00pm Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KARLHEINZ R SKOWRONEK/
Examiner, Art Unit 1631

1 September 2009